pollution on the rising trends of respiratory allergy and asthma

Effetti delle modificazioni climatiche e dell'inquinamento urbano sul trend in incremento delle patologie respiratorie allergiche e dell'asma

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ABSTRACT

Over the past two decades there has been increasing interest in studies regarding effects on human health of climate changes and urban air pollution. Climate change induced by anthropogenic warming of the earth's atmosphere is a daunting problem and there are several observations about the role of urbanization, with its high levels of vehicle emissions and other pollutants, and westernized lifestyle with respect to the rising frequency of respiratory allergic diseases observed in most industrialized countries.

There is also evidence that asthmatic subjects are at increased risk of developing exacerbations of bronchial obstruction with exposure to gaseous (ozone, nitrogen dioxide, sulfur dioxide) and particulate inhalable components of air pollution.

A change in the genetic predisposition is an unlikely cause of the increasing frequency in allergic diseases because genetic changes in a population require several generations. Consequently, environmental factors such as climate change and indoor and outdoor air pollution may contribute to explain the increasing frequency of respiratory allergy and asthma. Since concentrations of airborne allergens and air pollutants are frequently increased contemporaneously, an enhanced IgE-mediated response to aeroallergens and enhanced airway inflammation could account for the increasing frequency of allergic respiratory diseases and bronchial asthma.

Scientific societies such as the European Academy of Allergy and Clinical Immunology, European Respiratory Society and the World Allergy Organization have set up committees and task forces to produce documents to focalize attention on this topic, calling for prevention measures.

Keywords: **Air pollution, airway hyperreactivity, bronchial asthma, pollen allergy, respiratory allergy, thunderstorm-associated asthma, urban air pollution.**

RIASSUNTO

Nelle ultime due decadi si è registrato un crescente interesse sugli effetti delle modificazioni climatiche e dell'inquinamento urbano sulla salute dell'uomo. Le modificazioni climatiche indotte dal riscaldamento globale dell'atmosfera terrestre su base antropica rappresentano un problema pressante e si sono moltiplicate le osservazioni sul ruolo dell'urbanizzazione, con i suoi elevati livelli di emissioni di veicoli e di altri inquinanti, e dello stile di vita occidentale sulla sempre maggior frequenza di malattie respiratorie su base allergica nei paesi a più elevato tasso di industrializzazione.

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Vi è inoltre evidenza che gli asmatici sono a maggior rischio di sviluppo di riacutizzazioni dell'ostruzione bronchiale con l'esposizione alle componenti dell'inquinamento atmosferico di tipo gassoso (ozono, biossido di azoto, biossido di zolfo) e particolato. È improbabile che possa essere chiamata in causa una modificazione della predisposizione genetica per giustificare l'aumentata incidenza di malattie allergiche, perché le modificazioni genetiche richiedono diverse generazioni per esprimersi. Sono quindi i fattori ambientali come le modificazioni climatiche, l'inquinamento dell'ambiente esterno e domestico a potere spiegare almeno in parte la maggiore frequenza di malattie respiratorie su base allergica e di asma. Poiché le concentrazioni di allergeni inalati e di inquinamento atmosferico vanno spesso di pari passo, una maggior risposta IgE-mediata agli aeroallergeni ed una maggior flogosi delle vie aeree può dar conto della maggior frequenza di forme allergiche respiratorie e di asma bronchiale.
Le società scientifiche come la European Academy of Allergy and Clinical Immunology, la European Respiratory Society e la World Allergy Organization hanno organizzato comitati e task force per produrre documenti che mettono a fuoco questa materia, raccomandando misure di tipo preventivo.

Parole chiave: Allergia ai pollini, allergie respiratorie, asma bronchiale, asma associata ai temporali, inquinamento dell'aria, inquinamento urbano, iperreattività bronchiale.

INTRODUCTION

Evidence suggests that allergic respiratory diseases such as rhinitis and bronchial asthma have become more common worldwide over the past three decades [1-4]; in parallel, in the past few years, much etiological and pathogenic research has been carried out in an attempt to determine the causes of this rising frequency and significant improvements have been made in our knowledge concerning the effects of air pollution on human health. Several studies have shown the adverse effects of ambient air pollution on respiratory health [5-9] and scientific societies such as the European Academy of Allergy and Clinical Immunology, European Respiratory Society and World Allergy Organization have organized committees and task forces to produce documents on this issue [10-12].
About climate change it is now widely accepted that the earth's temperature is increasing, as confirmed by warming of the oceans, rising sea levels, glaciers melting, sea ice retreating in the Arctic and diminished snow cover in the Northern Hemisphere. Moreover, changes are also occurring in the amount, intensity, frequency and type of precipitation as well as the increase of extreme weather events, like heat waves, droughts, floods and hurricanes. The Working Group I to the 4th Assessment Report of the Intergovernmental Panel on Climate Change (IPCC) states "most of the observed increase in globally averaged temperatures since the mid-20th century is very likely due to the observed increase in anthropogenic greenhouse gas concentrations" [13]. However, observational evidence indicates that recent regional changes in climate, particularly temperature increases, have already affected a diverse set of physical and biological systems in many parts of the world [10,11,13].

Exposure to air pollution enhances the airway response to inhaled allergens in susceptible subjects. Indeed, in most industrialized countries people who live in urban areas tend to be more affected by allergic respiratory diseases than those in rural areas [14,15].
An individual's response to air pollution depends on the source and components of the pollution, as well as on climatic agents. Indeed, some air pollution-related episodes of asthma exacerbation are due to climatic factors that favour the accumulation of air pollutants at ground level [7,11] and some cities are continuously affected by black smog caused by motor vehicles. There is evidence that living near high traffic roads is associated with deterioration of respiratory health. Road traffic with its gaseous and particulate emissions is currently, and likely to remain for several years, the main contributor to air pollution in most urban areas [5-12,16,17].
Air pollution is associated with many signs of asthma exacerbation, e.g. increased bronchial hyperresponsiveness, increased medication use, and increased visits to emergency departments and hospital admissions [16-19]. Time series data show that traffic-related air pollution in urban areas has adverse effects on mortality from respiratory and cardiovascular disease [20-29].
The most abundant components of air pollution in urban areas with high levels of vehicle traffic are inhalable particulate matter (PM), nitrogen dioxide and ozone. The effects of air pollutants on lung function depend on the type of pollutant and its environmental concentration, the duration of exposure and the total ventilation of exposed persons. Aeroallergens, such as those derived from pollens and fungal spores in outdoor atmosphere, are able to induce bronchial obstruction in predisposed subjects and pollen allergy is widely used to study the interrelationship between air pollution and respiratory allergy in atopic subjects [27,30-33].
Airborne pollen grains, plant debris of very small size [31] and pollen grains ruptured during thunderstorms [32-36] can cause allergic respiratory symptoms in predisposed subjects. They also interact with other airborne contaminants in producing these effects.
There is a hypothesis that air pollutants promote airway sensitization by inducing changes in the allergenic content of airborne particles carrying allergens [29-33,37]. There is also evidence that airway mucosal damage and impaired mucociliary clearance induced by air pollution may facilitate the penetration and access of inhaled allergens to the cells of the immune system [29-33,37-40]. However, patients affected by asthma frequently experience rhinitis and thus they breathe through the mouth, bypassing the nasal function and so facilitating the penetration of pollutants and aeroallergens into the lower airways [40-42].

Air pollution of urban areas

The most abundant pollutants in the atmosphere of

urban areas are ozone, nitrogen dioxide and respirable PM. Sulphur dioxide is an addition of industrial areas. Aeroallergens are carried and delivered by fungal spores or by plant-derived particles (pollens, components of paucimicronic diameter and of vegetal nature, e.g. soybean dust, ricinus, etc.).

Ozone

Ozone is the main component of photochemical oxidants and "Summer smog", and probably accounts for up to 90% of total oxidant levels in cities that enjoy a mild sunny climate such as those of the Mediterranean area, California, etc. Ozone is generated at ground level by photochemical reactions involving ultraviolet radiations on atmospheric mixtures of nitrogen dioxide and hydrocarbons deriving from vehicle emissions. Safety standards for ozone levels are frequently exceeded in southern Europe, in particular in Mediterranean countries. About 40-60% of inhaled ozone is absorbed in the nasal airways, while the remainder reaches the lower airways and it can affect both the upper and lower respiratory tract.

Inhalation of high concentrations of ozone induces deterioration in lung function and increased airway reactivity to nonspecific and specific bronchoconstrictor agents and is related to an increased risk of asthma exhacerbation in asthmatic patients [43-52]. Increased atmospheric concentrations of ozone and nitrogen dioxide have been linked to increases in respiratory morbidity and in hospital admissions for asthma in children and adults [43-52]. Ozone exposure has also been reported to have a priming effect on allergen induced responses as well as an intrinsic inflammatory effect in the airways of allergic asthmatics [49-52]. Ozone produces an increase in intracellular reactive oxygen species and in epithelial cell permeability, which could facilitate penetration of inhaled allergens and toxins in the airways, so inducing an increased release of inflammatory mediators (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor [TNF]-alpha, etc.). Vagaggini et al. [51] showed that ozone's more dramatic effect in asthmatic subjects is most likely a result of existing chronic inflammation in the lower airways [51].

As the primary mechanism for ozone-induced decrements in FEV_1, a neurally-mediated inhibition of inspiratory effort involving C-fibres rather than bronchoconstriction has been proposed [45,52].

Because ozone-induced airway inflammation may last several days and ozone-related asthma exacerbations often occur several days after exposure, it seems feasible that ozone-induced enhancement of pre-existing airway inflammation enhances susceptibility to obstructive symptoms and asthma exacerbations.

It has long been hypothesized that ozone and other pollutants may increase the susceptibility of allergic individuals to antigens to which they are sensitized, and there are animal studies to support such an effect [49-52]. It has been reported that ozone is associated with an increased risk of asthma development among children in California playing outdoor sports. Thus, air pollution and outdoor exercise could contribute to the development of asthma in children by increasing airway inflammation and airway responsiveness [53].

Nitrogen dioxide

Like ozone, nitrogen dioxide is an oxidant pollutant, although it is less chemically reactive and thus probably less potent. Nitrogen dioxide (NO_2) is a precursor of photochemical smog, is found in outdoor air in urban and industrial regions and, in conjunction with sunlight and hydrocarbons, results in the production of ozone. Automobile exhaust is the most significant source of outdoor NO_2, although power plants and other sources that burn fossil fuels also release NO_2 into the environment. The most significant exposure to NO_2 occurs indoors in conjunction with the use of gas cooking stoves and kerosene space heaters. Most ambient NO_2 is generated by the burning of fossil-derived fuels. Outdoor levels of NO_2 are not usually associated with notable changes in bronchial function in asthmatic patients. Controlled exposure studies of subjects with asthma have produced inconsistent results regarding the ability of NO_2 to enhance nonspecific airway responsiveness with some evidence of a subgroup with increased sensitivity [54-56]. Results of epidemiologic studies suggest that exposure to NO_2 is associated with increased prevalence of asthma and rhinitis and with acute decrements in lung function in asthmatic subjects [57-60].

Sulphur dioxide

Sulphur dioxide is released into the atmosphere primarily as a result of industrial combustion of high-sulphur-containing coal and oil. It is primarily generated from the burning of sulphur-containing fossil fuel and it has been demonstrated to induce acute bronchoconstriction in asthmatic subjects at concentrations well below those required to induce this response in healthy subjects [61-63]. In contrast to ozone, the bronchoconstrictor effect of inhaled sulfur dioxide in individuals with asthma occurs after extremely brief periods of exposure, especially with oral breathing and high ventilatory rates, as in exercise [64-65]. Significant responses are observed within 2 minutes, maximal response is seen within 5 to 10 minutes. There can also be spontaneous recovery (30 minutes after challenge) and a refractory period of up to 4 hours, whereas repeated exposure to low levels of sulfur dioxide results in tolerance to subsequent exposure. Pharmacologic studies suggest that the effect is a cholinergically-mediated neural mechanism. Moreover, sulfur dioxide exposure enhances responses to other environmental agents that exacerbate bronchospasm.

Particulate matter

Particulate matter (PM) is the most serious air pollution problem in many cities and towns and it appears to be the component of air pollution most consistently associated with adverse health effects.

In other words, PM is a major component of urban air pollution. It is a mixture of solid and liquid particles of different origin, size and composition among which pollen grains and other vegetable particles carrying allergens and mold spores. Inhalable PM that can reach the lower airways is measured as PM_{10} (less than 10 μm in aerodynamic diameter) and $PM_{2.5}$ (less than 2.5 μms) [66-69]. Human lung parenchyma retains $PM_{2.5}$, while particles larger than 5 μm and < 10 μm only reach the proximal airways where they are eliminated by mucociliary clearance if the airway mucosa is intact [66-69]. In many geographical areas particulate air pollution is significantly associated with enhanced mortality from respiratory and cardiovascular diseases, exacerbation of allergic asthma, chronic bronchitis, respiratory tract infection and hospital admissions [20-29]. The World Health Organization estimates that inhalation of particulate matter is responsible for 500,000 excess deaths each year worldwide [1]. Seaton et al. [70] hypothesized that fine particulate matter found in urban areas, by penetrating deep into airways, is able to induce alveolar inflammation which is responsible for variation in blood coagulability and release of mediators favouring acute episodes of respiratory and cardiovascular diseases.This observation has been validated by recent studies [26-28].

To try to find an explanation for the acute respiratory effects associated with inhalable particulate matter, the same authors [71] suggested that transition metals in the particles damage airways thereby generating free radicals. In particular, iron, which generates hydroxyl radicals, seems to be responsible for the adverse respiratory effects [72]. Other transition metals (chromium, cobalt, copper, manganese, nickel, titanium, vanadium and zinc) derived from various urban or combustion source samples have also been correlated to radical activation and lung injury in animal experiments [73-75].

Diesel exhaust particulate

Diesel exhaust particulate (DEP) accounts for most of the airborne particulate matter (up to 90%) in the atmosphere of the world's largest cities [76]. It is characterized by a carbonaceous core in which 18,000 different high-molecular-weight organic compounds are adsorbed. DEP presents a large number of particles, about 100 times more particles per mile than petrol engines of equivalent power. Although diesel engines emit far less carbon dioxide than petrol engines, they emit over 10 times more nitrogen dioxide, aldehydes and respirable particulate matter than unleaded petrol engines and over 100 times more than engines fitted with catalytic converters [77]. DEP exerts its effect by way of specific activities of chemical agents, i.e. polyaromatic hydrocarbons. The particles are deposited on the mucosa of the airways, and by virtue of their hydrophobic nature, the aromatic hydrocarbons allow them to diffuse easily through cell membranes and bind to a cytosolic receptor complex. Through the subsequent nuclear action, aromatic hydrocarbons can modify the growth and the differentiation programmes of cells [77-78].

Acute exposure to diesel exhaust causes irritation of the nose and eyes, headache, lung function changes, respiratory changes, fatigue and nausea, while chronic exposure is associated with cough, sputum production and lung function decrements [77,79-84]. Experimental studies have shown that DEP causes respiratory symptoms and is able to modify the immune response in predisposed animals and humans [77,79-81]. In this context DEP seems to exert an adjuvant immunological effect on IgE synthesis in atopic subjects thereby influencing sensitization to airborne allergens. Rudell et al. [84] showed that healthy volunteers exposed to DEP had a greater number of alveolar macrophages, neutrophils and T lymphocytes in BAL than did controls. Other studies confirmed the effects favouring airway inflammation and demonstrated an atopy-enhancing effect of diesel exhaust [81-84]. Diaz-Sanchez et al. [81-82] studied the effect of DEP on antigen in ragweed-sensitive subjects challenged (nasal provocation test) with DEP, the major ragweed allergen (Amb a 1) and a combination of DEP and Amb a 1. Provocation with ragweed led to an increase in both total and ragweed-specific IgE in nasal lavage fluid measured 18 hours, 4 days and 8 days post-challenge. The DEP challenge increased the concentration of ragweed-specific IgE 16-fold versus concentrations observed after challenge with ragweed alone. The same authors showed that combined exhaust particulate and ragweed allergen challenge markedly enhances human *in vivo* nasal ragweed-specific IgE and skews cytokine production to a T-helper cell 2-type pattern [82]. All these results indicate that DEP plays a role in the enhanced allergic inflammatory response [77,79-84]. Regarding the DEP-related allergic respiratory disease, DEP can adsorb aeroallergens released by pollen grains and can prolong the retention of the allergen so as to provide for an enhanced IgE-mediated response [85]. The data on DEP are of particular interest in view of the increasing percentage of new cars with diesel engines in industrialized countries. Diesel-powered cars are usually promoted as being environmentally friendly because they produce up to 25% less carbon dioxide, which is a major contributor to global warming. The new diesel cars with new filters appear to reduce the production of PM at risk for exposed subjects.

Plant-derived allergens

Respiratory allergy induced by antigens released by pollen grains is very common [86]. For instance, between 8% and 35% of young adults in countries of the European Community have IgE serum antibodies to grass pollen allergens [87]. The cost of pollen allergy in terms of impaired work fitness, sick leave, physician visits and drug prescriptions is very high. Subjects living in urban areas tend to be more affected by plant-derived respiratory disorders than those living in rural areas [14,15]. Ishizaki et al. [88] observed that respiratory allergy was more

prevalent in subjects living near busy roads than in subjects living in areas with higher atmospheric concentrations of pollen allergens but with less traffic. Various studies suggest that there is an interaction between air pollutants and allergens that exacerbates the development of atopy and the respiratory symptoms of allergic disease. These results should be interpreted with caution because they can be affected by several factors that were not examined. In a time-series study Brunekreef et al. [27] found a strong association between the day-to-day variation in pollen concentrations and deaths due to cardiovascular disease, chronic obstructive pulmonary disease, and pneumonia.

To prevent pollen allergy, an ideal (but hardly feasible approach) is to minimize the risk of contact with these agents by moving to a non-risk area on the basis of pollen-calendars. Pollen grains are the primary carriers of pollen allergens, which explains why the symptoms typical of hay fever are located in the eyes, nose and nasopharynx. Differently, allergic asthma in pollen-sensitive patients is an enigma because intact pollen grains, which measure over 10 μm in diameter, are too large to enter the lower airways [31-33,89]. Moreover, in many instances peak asthma symptom scores differ temporally from peak pollen counts, and early morning symptoms sometimes precede later peaks in the daily pollen cycle. The etiology of pollen asthma and the discordance between pollen count and bronchial symptoms was partially explained with the identification of pollen allergens in microaerosol suspensions smaller than pollen grains [89], which could be present in atmosphere before the start and after the end of the season, so prolonging the respiratory symptoms of sensitized patients. By virtue of their small size, these paucimicronic particles can reach the peripheral airways with inhaled air, so inducing asthma in sensitized subjects. Thus, parts of an organism (in this case of vegetal nature) other than pollen grains or spores contain significant allergen concentrations that are readily disseminated via an airborne route. These allergenic paucimicronic particles act only as carriers for the protein agent with antigenic property that causes symptoms. Allergens have been detected in the leaves and stems of allergenic plants [9,32]. They may result from elution of allergens from pollen grains with their later dispersion in microdroplets.

It is important also to note that, starting with pollen, the interest in smaller airborne allergenic units now embraces a variety of agents (e.g. house dust, arthropod emanations, and animal allergens) of undefined or variable particle size [9,32]. The advent of high speed impingers, which are very efficient in collecting small aerosols on filters, has given impetus to the study of a variety of environmental agents, and antigenic activity has been identified in both micronic and submicronic fractions.

Thunderstorm-associated asthma in pollinosis patients

Suphioglu et al. [90] and Knox et al. [85] found that under wet conditions or during thunderstorms pollen grains may, after rupture by osmotic shock, release part of their content, including respirable, allergen-carrying starch granules (0.5-2.5 μm) into the atmosphere. 'Thunderstorm-associated asthma' was recognized over 15 years ago in Britain by Packe and Ayres [91], who described an association between a thunderstorm and an asthma outbreak with 26 asthmatic subjects treated in Birmingham Hospital in 36 hours compared with 2-3 cases in the same time interval in the days preceding the thunderstorm. Other asthma outbreaks during thunderstorms have been described in Melbourne, Australia [92,93]. Also, this phenomenon was followed by a rapid increase in hospital or general practitioner visits for asthma. No unusual levels of air pollution were noted at the time of these epidemics but there was a strong association with grass pollen. Grass pollens after rupture by osmotic shock during thunderstorms release large amounts of paucimicronic allergenic particles, i.e. cytoplasmatic starch granules containing grass allergens. Because of their very small size, starch granules can penetrate the lower airways and induce the appearance of bronchial allergic symptoms. Other thunderstorm-associated asthma outbreaks have been reported: in London on the night between 24 and 25 June 1994 [94], in Wagga Wagga, Australia on 30 October 1997 [95], and in Naples on June 4 2004 [9,71,96]. The asthma outbreak of London was the largest episode, with about 100 emergency visits to several hospitals of London and southwest England. Interestingly, in the London outbreak several patients examined, who were not known to be asthmatics or were affected only by seasonal rhinitis, experienced an asthma attack. This explains why grass induces mainly allergic rhinitis in sensitized atopic subjects. In fact, being more than 30 μm, intact grass pollen grains can only reach the lower airways after rupture.

During the episode of thunderstorm-associated asthma registered in Naples on 4 June 2004 (between 1.30 and 2.00 am), 6 adults (3 women and 3 men aged between 38 and 60 years) and a girl of 11 had attacks of severe bronchial asthma, which was nearly fatal in one case. All patients received treatment in emergency departments and one was admitted to an intensive care unit for very severe bronchial obstruction and acute respiratory insufficiency. However, also without outbreaks, frequently pollinosis patients experience a deterioration of their symptoms when thunderstorms or strong rains start.

Plant derived carriers of aeroallergens

Among vegetal small particles carrying allergens are the so-called Ubish bodies, paucimicronic spheroidal structures which develop in the anthers of higher plants [30,32,33,97,98]. Their function is unknown. They generally occur in large numbers, are usually only a few micrometers in diameter and can contain allergens. Ubish bodies may be involved in the dispersal of pollen and their size is op-

timal for penetration into lower airways.
Besides providing an explanation for bronchial asthma symptoms in pollinosis patients, a practical offshoot of these studies is that the traditional "pollen count" may be misleading as an index of outdoor allergen exposure in particular situations. In fact, the pollen count technique consists of examination of pollen grains collected in volumetric "pollen traps" under the microscope and the definition of their concentration per cubic meter of air, whereas immunochemical methods are required to identify the allergens carried by airborne microparticulate matter such as starch granules and Ubish bodies [33,97]. In an attempt to establish correlations with clinical symptoms and to estimate the different risks for asthma and hay fever in pollinosis subjects it would be interesting to quantify atmospheric variations in these biological aerosols and in their allergenic activity.

Other aeroallergens responsible for epidemic asthma in urban areas

Soybean dust could be responsible for outbreaks of severe asthma that were first attributed to urban air pollution. Examples are asthma epidemics in cities with large industrial port facilities such as Barcelona. From 1981 to 1987, 26 outbreaks of asthma with 11 deaths occurred in Barcelona without any apparent relation to air pollution [99-103]. The causal agent was subsequently found to be soybean dust released into the air during unloading of cargo into a harbour silo that was not equipped with a dust-control device. Antò and colleagues demonstrated that about 74% of epidemic cases had specific IgE antibodies versus a commercial soybean antigen in comparison with 4.6% of controls [99,101]. In addition, using the assays of urban aerosols collected with high-volume samplers and the RAST inhibition technique these authors showed highly significant differences in the atmospheric content of soybean antigens between days marked by the asthma epidemic and days free of an excess of asthma crisis. The strong association between airborne soybean dust and asthma outbreaks was reinforced by the results of studies showing high airborne concentrations on epidemic days and low values on nonepidemic days.
All these studies showed that asthma outbreaks were a "point-source" epidemic. Protective measures (i.e. cargo unloading after filters were fitted to the grain elevators) dramatically reduced airborne allergen levels of soybean dust and asthma-related visits to the emergency room [101]. The IgE serum levels in exposed subjects also progressively decreased.
In Naples, more than 100 patients were admitted to hospital for asthma on a single day in December 1993 [102]. This asthma outbreak coincided with the unloading of a cargo of soybean. Interestingly, neither in the Barcelona nor in the Naples outbreaks were there cases of severe asthma attacks in children.
When the asthma epidemic which occurred in New Orleans in 1969 [103,104] was reexamined [105], it was found that the number of asthma attacks was higher on days when ships carrying soybean were anchored in the harbour. Attacks were also higher in concomitance with air stagnation and with winds carrying particles from two grain elevators. No association was observed between asthma attacks and the presence of ships carrying wheat or corn.

Air pollution, climate changes and pollen-related respiratory allergy

We still have much to learn about the effects of other climatic factors that seem to be important for asthma, e.g. wind speed and transition of cold fronts. It is well known that inhalation of cold air reduces lung function in asthmatics thus favouring bronchoconstriction. Moreover, exercise in polluted areas results in greater deposition of air pollutants, including allergen-carrying allergens, in the lower airways. Exercise increases oral breathing, total ventilation and inertial impaction of inhaled particles in the airways. The role of climatic factors (e.g. barometric pressure, temperature and humidity) in triggering and/or exacerbating respiratory allergic symptoms in predisposed subjects is still poorly understood and asthma attacks have been linked with both low and high atmospheric pressure. More studies are required to clarify the role of weather in morbidity and mortality for respiratory allergy.
There is also the thorny question as to how increasing levels of greenhouse gases and concomitant climate changes will influence the frequency and severity of pollen-induced respiratory allergy. A variety of direct and indirect evidence suggests that climate changes may affect pollen release and consequently pollen-related asthma [9,11,12]. Climate variations are likely to influence vegetation with consequent changes in growth, reproductive cycle, etc. as well as in the production of allergenic pollen (seasonal period and intensity) with a greater proliferation of weed species. Climate changes vary from region to region: some areas will be subject to increases in ultraviolet radiation and or rainfall frequency and other areas to reductions.
In Italy in the 20 years from 1981 to 2000 the average mean temperature has increased by about 0.6°C: this warming is accompanied by an average reduction of 15% in rainfall, and the rain is concentrated is a shorter period causing more violent rainstorms [106]. How are allergenic plants responding to these changes? The increased temperature in winter and spring has brought about early pollination, and the increased summer temperature has resulted in a prolonging of the pollination of herbaceous, allergenic plants. Pollen seasons, and therefore seasonal allergic symptoms, tend to be longer in warmer years. The prolonging of autumn could prolong the presence of fungal spores in the atmosphere. Due to the 'urban climate effect' (heating caused by high building density and soil sealing), pollination can occur 2-4 days earlier in urban than in rural areas.
Vegetation reacts with air pollution over a wide

range of environmental conditions and pollutant concentrations. Several factors influence the interaction, including type of air pollutant, plant species, nutrient balance, soil conditions and climatic factors. At low levels of exposure for a given species and pollutant, no significant effect is observed. However, as the exposure level increases, there may be biochemical alterations of the plants [107-110]. Plants can absorb pollutants through the leaves or through the root system. In the latter case, deposition of air pollutants on soils can alter the nutrient content of soil in the proximity of the plant thus leading to indirect or secondary effects of air pollutants on vegetation. Metabolic variations affect the plant's structural integrity and there are probably changes in the pollen proteins, including those acting as allergens.

Air pollution can influence the plant allergenic content, and by affecting plant growth it can affect both the amount of pollen produced and the amount of allergenic proteins contained in pollen grains. The pollen of plants stressed by air pollution express enhanced levels of allergenic proteins [109]. Pollen grains collected from roadsides with heavy traffic and from other areas with high levels of air pollution are covered with large numbers of microparticulates (usually less than 5 μm in diameter) and there is a hypothesis that interaction between air pollution components and pollen allergens alters the antigenicity of pollen allergens.

CONCLUSIONS

Both the prevalence and severity of respiratory allergic diseases such as rhinitis and bronchial asthma have increased in recent years and indoor and outdoor air pollution and climate changes are implicated in this increasing frequency. Increasing production of CO_2 with climate changes, urbanization with its high levels of vehicle emissions and westernized lifestyle parallel the increase in respiratory allergy in most industrialized countries. People living in urban areas tend to be more affected by the disease, than those living in rural areas. In atopic subjects, exposure to air pollution increases airway responsiveness to aeroallergens. Pollen grains, seem to be a useful model to study the interrelationship between air pollution and respiratory allergic diseases, and in atmosphere and in the airways an interaction has been observed between pollen allergens and air pollution [106-110]. By adhering to the surface of pollen grains, components of air pollution could modify their antigenic properties. However, the airway mucosal damage and the impaired mucociliary clearance induced by air pollution may facilitate the penetration and the access of inhaled allergens to the cells of the immune system, and so promote airway sensitization. Consequently an increased IgE-mediated response to aeroallergens and enhanced airway inflammation favoured by air pollution could account for the increasing prevalence of allergic respiratory diseases in urban areas. Among the measures for reducing air pollution and its effects are:

- reducing the private traffic in towns by promoting public transportation;
- controlling vehicle emissions;
- planting in urban areas non-allergenic trees such as *pinaceae*, *palmaceae* and *ulmaceae*, avoiding *cupressaceae*, *betulaceae* and *oleaceae* [11,86].

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